

CLAIMS

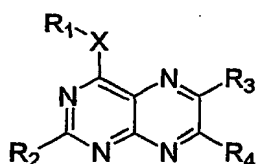
1. Use of a pteridine derivative for the manufacture of a medicament for the prevention or treatment of a disorder in a mammal, the said disorder being selected from the group consisting of:

- 5
- septic or endotoxic shock,
 - TNF- α - mediated diseases,
 - pathologies and conditions associated with and/or induced by abnormal levels of TNF- α occurring in a systemic, localized or particular tissue type or location in the body of the mammal,

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 - toxic effects of TNF- α and/or anti-cancer chemotherapeutic agents,
 - injuries after irradiation of a tissue of the mammal by radio-elements, and
 - cachexia,

the said pteridine derivative having the general formula (I):



15 wherein X represents an oxygen atom or a group with the formula S(O)_m wherein m is an integer from 0 to 2, or a group with the formula NZ and wherein:

- R₁ is a group selected from the group consisting of C₁₋₇ alkyl, C₂₋₇ alkenyl, C₂₋₇ alkynyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, aryl, alkylaryl, arylalkyl, heterocyclic, heterocyclic-substituted alkyl and alkyl-substituted heterocyclic, each of said groups being optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₄ alkyl, C₁₋₄ alkoxy, C₂₋₇ alkenyl, C₂₋₇ alkynyl, halo C₁₋₄ alkyl, C₃₋₁₀ cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxyl, sulfhydryl, nitro, hydroxylamino, mercaptoamino, cyano, carboxylic acid or esters or thioesters or amides or thioamides or halides or anhydrides thereof, thiocarboxylic acid or esters or thioesters or amides or thioamides or halides or anhydrides thereof, carbamoyl, thiocarbamoyl, ureido, thio-ureido, amino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxylalkylamino, mercaptoalkyl-amino, heterocyclic amino, hydrazino, alkylhydrazino and phenyl-hydrazino; or R₁ is a carboxyalkyl, carboxyaryl, thiocarboxyaryl or thiocarboxyalkyl group;
- Z is a group independently defined as R₁ or Z is hydrogen or the group NZ together with R₁ is either hydroxylamino or an optionally substituted heterocyclic group containing at least one nitrogen atom;

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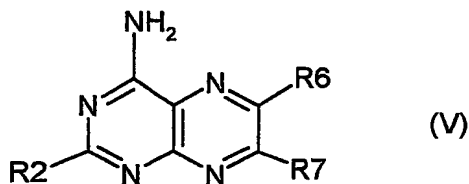
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- R₂ is selected from the group consisting of amino; acylamino; thioacylamino; carbamoyl; thiocarbamoyl, ureido; thioureido, sulfon-amido; hydroxylamino; alkoxyamino; thioalkylamino; mercaptoamino, hydrazino; alkylhydrazino; phenylhydrazino; optionally substituted heterocyclic radicals; C₁₋₇ alkylamino; arylamino; arylalkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; heterocyclic amino; hydroxyalkylamino; mercaptoalkylamino; C₁₋₇ alkoxy; C₃₋₁₀ cycloalkoxy; thio C₁₋₇ alkyl; arylsulfoxide; arylsulfone; heterocyclic sulfoxide; heterocyclic sulfone; thio C₃₋₁₀ cycloalkyl; aryloxy; arylthio; arylalkyloxy; arylalkylthio; oxyheterocyclic and thioheterocyclic radicals,
 - R₄ is an atom or a group selected from the group consisting of hydrogen; halogen; C₁₋₇ alkyl; C₂₋₇ alkenyl; C₂₋₇ alkynyl; halo C₁₋₇ alkyl; carboxy C₁₋₇ alkyl; acetoxy C₁₋₇ alkyl; carboxyaryl; C₁₋₇ alkoxy; C₃₋₁₀ cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C₁₋₇ alkyl; thio C₃₋₁₀ cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; amino; hydroxylamino; mercapto-amino; acylamino; thioacylamino; alkoxyamino; thioalkylamino; acetal; thioacetal; carboxylic acid; carboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; hydroxyl; sulfhydryl; nitro; cyano; carbamoyl; thiocarbamoyl, ureido; thio-ureido; alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynyl-amino; arylamino; arylalkylamino; hydroxyalkylamino; mercapto-alkylamino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkylloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters, thioesters, halides, anhydrides, amides and thioamides thereof; aryl groups optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, C₂₋₇ alkenyl, C₂₋₇ alkynyl, halo C₁₋₇ alkyl, nitro, hydroxyl, sulfhydryl, amino, C₃₋₁₀ cycloalkoxy, aryloxy, arylalkyloxy, oxyhetero-cyclic, heterocyclic-substituted alkyloxy, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, carbamoyl, thiocarbamoyl, ureido, thio-ureido, sulfonamido, hydroxylamino, alkoxyamino, mercaptoamino, thioalkylamino, acylamino, thioacylamino, cyano, carboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, thiocarboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkyl-hydrazino and phenylhydrazino; optionally substituted heterocyclic radicals; aromatic or heterocyclic substituents substituted with an aliphatic spacer between the pteridine ring and the aromatic or heterocyclic substituent, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 1 to 4 carbon atoms which may contain one or more functions, atoms or radicals

- selected from the group consisting of carbonyl (oxo), thiocarbonyl, alcohol (hydroxyl), thiol, ether, thio-ether, acetal, thio-acetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, acylamino, thioacylamino, carbamoyl, thiocarbamoyl, ureido, thio-ureido, carboxylic acid or ester or thioester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercaptoamino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenyl-amino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl, sulfonamido and halogen; branched or straight, saturated or unsaturated aliphatic chains of 1 to 7 carbon atoms optionally containing one or more functions selected from the group consisting of carbonyl (oxo), thiocarbonyl, alcohol (hydroxyl), thiol, ether, thio-ether, acetal, thio-acetal, amino, imino, oximino, alkyl-oximino, amino-acid, cyano, acylamino; thioacylamino; carbamoyl, thiocarbamoyl, ureido, thio-ureido, carboxylic acid ester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercapto-amino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynyl-amino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl, sulfonamido and halogen; and
- R₃ is an atom or a group defined as R₄, or R₃ together with R₄ forms a homocyclic or heterocyclic radical;

or having the general formula (V):



wherein:

- R₂ is selected from the group consisting of nitrogen-containing heterocyclic radicals other than morpholinyl and piperazinyl, said nitrogen-containing heterocyclic radicals being attached to the pteridine ring by means of a nitrogen atom; arylalkylamino; arylamino; heterocyclic-substituted alkylamino; C₁₋₇ alkoxy; aryloxy; arylthio; arylsulfonyl; arylalkyloxy; arylalkylthio; C₁₋₇ alkylsulfonyl; heterocyclic-substituted alkyloxy; and heterocyclic-substituted alkylthio;
- R₆ and R₇ are independently selected from the group consisting of hydrogen; halogen; C₁₋₇ alkyl; C₂₋₇ alkenyl; C₂₋₇ alkynyl; halo C₁₋₇ alkyl; carboxy C₁₋₇ alkyl; C₁₋₇ alkylsulfonyl; carboxyaryl; C₁₋₇ alkoxy; C₃₋₁₀ cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; C₁₋₇ alkylthio; thio C₃₋₁₀ cycloalkyl; arylthio; arylsulfonyl;

thio-heterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino; mercaptoamino; acylamino; thioacylamino; alkoxyamino; thioalkylamino; acetal; thio-acetal; carboxylic acid; carboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; hydroxyl; sulfhydryl; nitro; cyano; carbamoyl; thiocarbamoyl; ureido; thioureido; amino; alkyl-amino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynyl-amino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkyl-amino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkyloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters, thioesters, halides, anhydrides, amides and thioamides thereof; aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C₁₋₇ alkyl, C₂₋₇ alkenyl, C₂₋₇ alkynyl, halo C₁₋₇ alkyl, nitro, hydroxyl, sulfhydryl, amino, C₁₋₇ alkoxy, C₃₋₁₀ cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, thioaryl, thio-heterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, C₁₋₇ alkanoyl (acyl), carbamoyl, thiocarbamoyl, ureido, thioureido, sulfonamido, hydroxyl-amino, alkoxyamino, mercaptoamino, thioalkylamino, acylamino, thioacylamino, cyano, carboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, thiocarboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino and phenylhydrazino; optionally substituted heterocyclic radicals; aryl or heterocyclic radicals substituted with an aliphatic spacer between the pteridine ring and said aryl or heterocyclic radical, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 1 to 4 carbon atoms which may contain one or more functions, atoms or radicals independently selected from the group consisting of carbonyl, thiocarbonyl, hydroxyl, thiol, ether, thioether, acetal, thioacetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, acylamino, thioacyl-amino, carbamoyl, thiocarbamoyl, ureido, thio-ureido, carboxylic acid or ester or thioester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercaptoamino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl, sulfonamido and halogen; branched or straight, saturated or unsaturated aliphatic chains of 1 to 7 carbon atoms optionally containing one or more functions, atoms or radicals independently selected from the group consisting of halogen, carbonyl, thiocarbonyl, hydroxyl, thiol, ether, thio-ether, acetal, thio-acetal, amino, imino, oximino, alkyloximino, aminoacid, cyano, acylamino,

- thioacylamino, carbamoyl, thiocarbamoyl, ureido, thioureido, carboxylic acid ester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercapto-amino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl and sulfonamido; or R₆ together with R₇ and the carbon atoms in positions 6 and 7 of the pteridine ring forms a homocyclic or heterocyclic radical;
- and/or being a pharmaceutically acceptable addition salt thereof and/or a stereoisomer thereof and/or a mono- or a di-*N*-oxide thereof and/or a solvate and/or a dihydro- or tetrahydropteridine derivative thereof.
2. Use according to claim 1, wherein the pteridine derivative has the general formula (I) and wherein R₁ is selected from the group consisting of methyl, ethyl, isopropyl and pentyl.
 3. Use according to claim 1, wherein the pteridine derivative has the general formula (I) and wherein R₃ is 3-thienyl, 2-thienyl or a phenyl group with one or more substituents.
 4. Use according to claim 1, wherein the pteridine derivative has the general formula (I) and wherein R₃ is a phenyl group with one or more substituents each independently selected from the group consisting of fluoro, methoxy, ethoxy, trifluoromethyl, dimethylamino, chloro, cyano, methyl, ethyl, carboxymethyl, methylthio, dimethylcarboxamido, diethylcarboxamido and methylcarboxylate.
 5. Use according to claim 1, wherein the pteridine derivative has the general formula (I) and wherein:
 - X is NZ,
 - Z is selected from the group consisting of hydrogen, methyl, ethyl, n-propyl and benzyl, and
 - R₁ is selected from the group consisting of methyl, ethyl, n-propyl and benzyl.
 6. Use according to claim 1, wherein the pteridine derivative has the general formula (I) and wherein X is NZ and wherein the group NZ together with R₁ is selected from the group consisting of tetrahydropyridinyl, hydroxylamino, morpholinyl, piperidinyl, piperazinyl, 1,2,4-triazolyl and N-methylpiperazinyl.

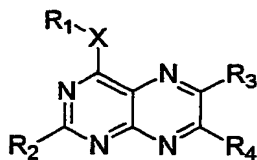
7. Use according to claim 1, wherein the pteridine derivative has the general formula (I) and is a compound selected from the group consisting of:
- 2-amino-4-ethoxypteridine
 - 2-amino-4-ethoxy-6-chloro-pteridine
 - 5 - 2-amino-4-ethoxy-6-(4-methoxyphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(2-methoxyphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(3-methoxyphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(3,4-difluorophenyl)-pteridine
 - 2-amino-4-ethoxy-6-(4-dimethylaminophenyl)-pteridine
 - 10 - 2-amino-4-ethoxy-6-(4-trifluoromethylphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(2-thienyl)-pteridine
 - 2-amino-4-ethoxy-6-(3-thienyl)-pteridine
 - 2-amino-4-ethoxy-6-(3,4-dichlorophenyl)-pteridine
 - 2-amino-4-ethoxy-6-(4-cyanophenyl)-pteridine
 - 15 - 2-amino-4-ethoxy-6-(4-ethoxyphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(4-fluorophenyl)-pteridine
 - 2-amino-4-ethoxy-6-(4-ethylphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(4-acetylphenyl)-pteridine
 - 2-amino-4-ethoxy-6-(3-fluoro-4-methylphenyl)-pteridine
 - 20 - 2-amino-4-ethoxy-6-(4-methylthiophenyl)-pteridine
 - 2-amino-4-ethoxy-6-(4-N,N-dimethylbenzamido)-pteridine
 - 2-amino-4-isopropoxypteridine
 - 2-amino-4-isopropoxy-6-chloropteridine
 - 2-amino-4-isopropoxy-6-(3-methyl-4-methoxyphenyl)-pteridine
 - 25 - 2-amino-4-isopropoxy-6-(3,4-dimethylphenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(3-chloro-4-trifluoromethylphenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(3-chloro-4-fluorophenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(4-N,N-diethylbenzamido)-pteridine
 - 2-amino-4-isopropoxy-6-(4-trifluoromethylphenyl)-pteridine
 - 30 - 2-amino-4-isopropoxy-6-(3,4-difluorophenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(4-methoxyphenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(4-ethoxyphenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(4-N,N-dimethylbenzamido)-pteridine
 - 2-amino-4-isopropoxy-6-(3-thienyl)-pteridine
 - 35 - 2-amino-4-isopropoxy-6-(4-cyanophenyl)-pteridine
 - 2-amino-4-isopropoxy-6-(4-benzoic acid methyl ester)-pteridine
 - 2-amino-4-isopropoxy-6-(4-acetylphenyl)-pteridine

- 2-amino-4-isopropoxy-6-(3,4-dimethoxyphenyl)-pteridine
- 2-amino-4-ethylthio-6-(3,4-dimethoxyphenyl)-pteridine
- 2-amino-4-isopropylthio-6-(3,4-dimethoxyphenyl)-pteridine
- 2-amino-4-pentoxy-6-styrylpteridine,
- 5 - 2-amino-4-n-pentoxy-6-(1,2-dibromo-2-phenylethyl)-pteridine,
- 2-amino-4-methoxy-6-styryl-7-methoxypteridine,
- 2,4-diamino-6-phenyl-7-methylpteridine,
- 2-amino-4-dimethylamino-6-phenylpteridine,
- 2-amino-4-dimethylamino-6-(4-tolyl)pteridine,
- 10 - 2-amino-4-dimethylamino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-diethylamino-6-phenylpteridine,
- 2-amino-4-diethylamino-6-(4-chlorophenyl)pteridine,
- 2-amino-4-diethylamino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-diethylamino-6-(3,4-dimethoxyphenyl)pteridine,
- 15 - 2-amino-4-dibenzylamino-6-phenyl pteridine,
- 2-amino-4-dibenzylamino-6-(4-chlorophenyl)pteridine,
- 2-amino-4-dibenzylamino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-dibenzylamino-6-(3,4-dimethoxyphenyl)pteridine,
- 2-amino-4-dipropylamino-6-phenylpteridine,
- 20 - 2-amino-4-dipropylamino-6-(4-chlorophenyl)pteridine,
- 2-amino-4-dipropylamino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-dipropylamino-6-(3,4-dimethoxyphenyl)pteridine,
- 2-amino-4-morpholino-6-phenylpteridine,
- 2-amino-4-morpholino-6-(4-chlorophenyl)pteridine,
- 25 - 2-amino-4-morpholino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-morpholino-6-(3,4-dimethoxyphenyl)pteridine,
- 2-amino-4-piperidino-6-phenylpteridine,
- 2-amino-4-piperidino-6-(4-chlorophenyl) pteridine,
- 2-amino-4-piperidino-6-(4-methoxyphenyl)pteridine,
- 30 - 2-amino-4-piperidino-6-(3,4-dimethoxyphenyl)pteridine,
- 2-amino-4-N-methylpiperazino-6-phenylpteridine,
- 2-amino-4-N-methylpiperazino-6-(4-chlorophenyl)pteridine,
- 2-amino-4-N-methylpiperazino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-methylpiperazino-6-(3,4-dimethoxyphenyl)pteridine,
- 35 - 2-amino-4-pyrrolidino-6-(4-methoxyphenyl)pteridine,
- 2-amino-4-piperazino-6-phenylpteridine,
- 2-amino-4-piperazino-6-(4-chlorophenyl)pteridine,

- 2-amino-4-piperazino-6-(4-methoxyphenyl)pteridine,
 - 2-amino-4-piperazino-6-(3,4-dimethoxyphenyl)pteridine,
 - 2-amino-4-dibenzylamino-6-(3,4,5-trimethoxyphenyl)pteridine,
 - 2-amino-4-morpholino-6-(3,4,5-trimethoxyphenyl)pteridine,
 - 5 - 2-amino-4-(3-adamantylamino)-6-(3,4,5-trimethoxyphenyl)pteridine,
 - 2-amino-4-(3-adamantylamino)-6-naphtylpteridine,
 - 2-amino-4-(4-adamantylamino)-6-(3,4,5-trimethoxyphenyl)pteridine,
 - 2-amino-4-(4-adamantylamino)-6-naphtylpteridine,
 - 2-amino-4-morpholino-6-(3,4-formylidene-3,4-dihydroxyphenyl)pteridine,
 - 10 - 2-amino-4-dimethylamino-6-(3,4-formylidene-3,4-dihydroxyphenyl) pteridine,
 - 2-amino-4-pyrrolidino-6-(3,4-dimethoxyphenyl)pteridine,
 - 2-amino-4-dimethylamino-6-(3,4-dimethoxyphenyl)pteridine,
 - 2-amino-4-dimethylamino-6-methylpteridine,
 - 2-amino-4-ethoxy-6-phenylpteridine,
 - 15 - 2-amino-4-propylamino-6-phenylpteridine,
 - 2-amino-4-propylamino-6-(3,4-dimethoxyphenyl)pteridine,
 - 2-acetamido-4-hydroxy-6-(3,4-dimethoxyphenyl)pteridine,
 - 2-acetamido-4-isopropoxy-6-(3,4-dimethoxyphenyl)pteridine,
 - 2-amino-4-ethoxy-6-(3,4-dimethoxyphenyl)pteridine, and
 - 20 - 2-amino-4-(1,2,3,6-tetrahydropyridinyl)-6-(3,4-dimethoxyphenyl)pteridine.
8. Use according to any of claims 1 to 7, wherein the said disorder is septic shock and the medicament is for the treatment of a mammal with a serum level of interleukin-6 above 1,000 pg/ml at start of treatment.
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9. Use according to any of claims 1 to 7, wherein the said TNF- α -mediated disease is selected from the group consisting of neurodegenerative diseases, myelodysplastic syndromes and alcohol-induced hepatitis.
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10. Use according to any of claims 1 to 7, wherein the abnormal levels of TNF- α are levels exceeding by at least 10 % and at most 500% the TNF- α level present in a normal healthy subject.
11. A method of prevention or treatment of a disorder selected from the group consisting of:
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- septic or endotoxic shock,
 - TNF- α - mediated diseases,

- pathologies and conditions associated with and/or induced by abnormal levels of TNF- α occurring in a systemic, localized or particular tissue type or location in the body of the mammal,
- toxic effects of TNF- α and/or anti-cancer chemotherapeutic agents,
- 5 - injuries after irradiation of a tissue of the mammal by radio-elements, and
- cachexia,

comprising administering to the patient in need thereof an effective amount of a pteridine derivative having the general formula (I):



10 wherein X represents an oxygen atom or a group with the formula $S(O)_m$ wherein m is an integer from 0 to 2, or a group with the formula NZ and wherein:

- R_1 is a group selected from the group consisting of C_{1-7} alkyl, C_{2-7} alkenyl, C_{2-7} alkynyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, aryl, alkylaryl, arylalkyl, heterocyclic, heterocyclic-substituted alkyl and alkyl-substituted heterocyclic, each of said groups being optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-4} alkyl, C_{1-4} alkoxy, C_{2-7} alkenyl, C_{2-7} alkynyl, halo C_{1-4} alkyl, C_{3-10} cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C_{1-7} alkyl, thio C_{3-10} cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, hydroxyl, sulfhydryl, nitro, hydroxylamino, mercaptoamino, cyano, carboxylic acid or esters or thioesters or amides or thioamides or halides or anhydrides thereof, thiocarboxylic acid or esters or thioesters or amides or thioamides or halides or anhydrides thereof, carbamoyl, thiocarbamoyl, ureido, thio-ureido, amino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkyl-amino, hydroxylalkylamino, mercaptoalkyl-amino, heterocyclic amino, hydrazino, 25 alkylhydrazino and phenyl-hydrazino; or R_1 is a carboxyalkyl, carboxyaryl, thiocarboxyaryl or thiocarboxyalkyl group;
- Z is a group independently defined as R_1 or Z is hydrogen or the group NZ together with R_1 is either hydroxylamino or an optionally substituted heterocyclic group containing at least one nitrogen atom;
- 30 - R_2 is selected from the group consisting of amino; acylamino; thioacylamino; carbamoyl; thiocarbamoyl, ureido; thioureido, sulfon-amido; hydroxylamino; alkoxyamino; thioalkylamino; mercaptoamino, hydrazino; alkylhydrazino; phenylhydrazino; optionally substituted heterocyclic radicals; C_{1-7} alkylamino; arylamino; arylalkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; heterocyclic amino;

hydroxyalkylamino; mercaptoalkylamino; C₁₋₇ alkoxy; C₃₋₁₀ cycloalkoxy; thio C₁₋₇ alkyl; arylsulfoxide; arylsulfone; heterocyclic sulfoxide; heterocyclic sulfone; thio C₃₋₁₀ cycloalkyl; aryloxy; arylthio; arylalkyloxy; arylalkylthio; oxyheterocyclic and thioheterocyclic radicals,

5 - R₄ is an atom or a group selected from the group consisting of hydrogen; halogen; C₁₋₇ alkyl; C₂₋₇ alkenyl; C₂₋₇ alkynyl; halo C₁₋₇ alkyl; carboxy C₁₋₇ alkyl; acetoxy C₁₋₇ alkyl; carboxyaryl; C₁₋₇ alkoxy; C₃₋₁₀ cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; thio C₁₋₇ alkyl; thio C₃₋₁₀ cycloalkyl; thioaryl; thioheterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; amino; hydroxylamino; mercapto-amino; acylamino; thioacylamino; alkoxyamino; thioalkylamino; acetal;

10 thioacetal; carboxylic acid; carboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; hydroxyl; sulfhydryl; nitro; cyano; carbamoyl; thiocarbamoyl, ureido; thio-ureido; alkylamino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynyl-amino; arylamino; arylalkylamino; hydroxyalkylamino;

15 mercapto-alkylamino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkyloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters, thioesters, halides, anhydrides, amides and thioamides thereof; aryl groups optionally substituted with one or more substituents selected from the group consisting of halogen, C₁₋₇ alkyl, C₁₋₇ alkoxy, C₂₋₇ alkenyl, C₂₋₇ alkynyl, halo C₁₋₇ alkyl, nitro, hydroxyl, sulfhydryl,

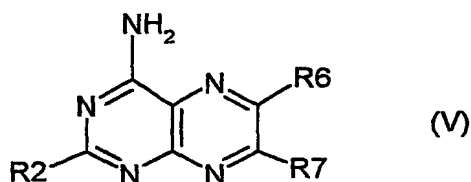
20 amino, C₃₋₁₀ cycloalkoxy, aryloxy, arylalkyloxy, oxyhetero-cyclic, heterocyclic-substituted alkyloxy, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, thioaryl, thioheterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, carbamoyl, thiocarbamoyl, ureido, thio-ureido, sulfonamido, hydroxylamino, alkoxyamino, mercaptoamino, thioalkylamino, acylamino, thioacylamino, cyano, carboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, thiocarboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkyl-hydrazino and phenylhydrazino; optionally substituted heterocyclic radicals; aromatic or heterocyclic substituents substituted with an

30 aliphatic spacer between the pteridine ring and the aromatic or heterocyclic substituent, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 1 to 4 carbon atoms which may contain one or more functions, atoms or radicals selected from the group consisting of carbonyl (oxo), thiocarbonyl, alcohol (hydroxyl), thiol, ether, thio-ether, acetal, thio-acetal, amino, imino, oximino, alkyloximino, amino-

35 acid, cyano, acylamino, thioacylamino, carbamoyl, thiocarbamoyl, ureido, thio-ureido, carboxylic acid or ester or thioester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀

- cycloalkyl, hydroxylamino, mercaptoamino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenyl-amino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl, sulfonamido and halogen; branched or straight, saturated or unsaturated
- 5 aliphatic chains of 1 to 7 carbon atoms optionally containing one or more functions selected from the group consisting of carbonyl (oxo), thiocarbonyl, alcohol (hydroxyl), thiol, ether, thio-ether, acetal, thio-acetal, amino, imino, oximino, alkyl-oximino, amino-acid, cyano, acylamino; thioacylamino; carbamoyl, thiocarbamoyl, ureido, thio-ureido, carboxylic acid ester or halide or anhydride or amide, thiocarboxylic acid or ester or
- 10 thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercapto-amino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynyl-amino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl, sulfonamido and halogen; and
- 15 - R₃ is an atom or a group defined as R₄, or R₃ together with R₄ forms a homocyclic or heterocyclic radical;

or having the general formula (V):



wherein:

- 20 - R₂ is selected from the group consisting of nitrogen-containing heterocyclic radicals other than morpholinyl and piperaziny, said nitrogen-containing heterocyclic radicals being attached to the pteridine ring by means of a nitrogen atom; arylalkylamino; arylamino; heterocyclic-substituted alkylamino; C₁₋₇ alkoxy; aryloxy; arylthio; arylsulfonyl; arylalkyloxy; arylalkylthio; C₁₋₇ alkylsulfonyl; heterocyclic-substituted alkyloxy; and heterocyclic-substituted alkylthio;
- 25 - R₆ and R₇ are independently selected from the group consisting of hydrogen; halogen; C₁₋₇ alkyl; C₂₋₇ alkenyl; C₂₋₇ alkynyl; halo C₁₋₇ alkyl; carboxy C₁₋₇ alkyl; C₁₋₇ alkylsulfonyl; carboxyaryl; C₁₋₇ alkoxy; C₃₋₁₀ cycloalkoxy; aryloxy; arylalkyloxy; oxyheterocyclic; heterocyclic-substituted alkyloxy; C₁₋₇ alkylthio; thio C₃₋₁₀ cycloalkyl; arylthio; arylsulfonyl; thio-heterocyclic; arylalkylthio; heterocyclic-substituted alkylthio; hydroxylamino;
- 30 mercaptoamino; acylamino; thioacylamino; alkoxyamino; thioalkylamino; acetal; thio-acetal; carboxylic acid; carboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; thiocarboxylic acid; thiocarboxylic acid esters, thioesters, halides, anhydrides, amides and thioamides; hydroxyl; sulfhydryl; nitro; cyano; carbamoyl; thiocarbamoyl;

ureido; thioureido; amino; alkyl-amino; cycloalkylamino; alkenylamino; cycloalkenylamino; alkynyl-amino; arylamino; arylalkylamino; hydroxyalkylamino; mercaptoalkyl-amino; heterocyclic amino; heterocyclic-substituted alkylamino; oximino; alkyloximino; hydrazino; alkylhydrazino; phenylhydrazino; cysteinyl acid, esters, thioesters, halides, anhydrides, amides and thioamides thereof; aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, C₁₋₇ alkyl, C₂₋₇ alkenyl, C₂₋₇ alkynyl, halo C₁₋₇ alkyl, nitro, hydroxyl, sulfhydryl, amino, C₁₋₇ alkoxy, C₃₋₁₀ cycloalkoxy, aryloxy, arylalkyloxy, oxyheterocyclic, heterocyclic-substituted alkyloxy, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, thioaryl, thio-heterocyclic, arylalkylthio, heterocyclic-substituted alkylthio, formyl, C₁₋₇ alkanoyl (acyl), carbamoyl, thiocarbamoyl, ureido, thioureido, sulfonamido, hydroxyl-amino, alkoxyamino, mercaptoamino, thioalkylamino, acylamino, thioacylamino, cyano, carboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, thiocarboxylic acid or esters or thioesters or halides or anhydrides or amides thereof, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino and phenylhydrazino; optionally substituted heterocyclic radicals; aryl or heterocyclic radicals substituted with an aliphatic spacer between the pteridine ring and said aryl or heterocyclic radical, whereby said aliphatic spacer is a branched or straight, saturated or unsaturated aliphatic chain of 1 to 4 carbon atoms which may contain one or more functions, atoms or radicals independently selected from the group consisting of carbonyl, thiocarbonyl, hydroxyl, thiol, ether, thioether, acetal, thioacetal, amino, imino, oximino, alkyloximino, amino-acid, cyano, acylamino, thioacyl-amino, carbamoyl, thiocarbamoyl, ureido, thio-ureido, carboxylic acid or ester or thioester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercaptoamino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino, hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl, sulfonamido and halogen; branched or straight, saturated or unsaturated aliphatic chains of 1 to 7 carbon atoms optionally containing one or more functions, atoms or radicals independently selected from the group consisting of halogen, carbonyl, thiocarbonyl, hydroxyl, thiol, ether, thio-ether, acetal, thio-acetal, amino, imino, oximino, alkyloximino, aminoacid, cyano, acylamino, thioacylamino, carbamoyl, thiocarbamoyl, ureido, thioureido, carboxylic acid ester or halide or anhydride or amide, thiocarboxylic acid or ester or thioester or halide or anhydride or amide, nitro, thio C₁₋₇ alkyl, thio C₃₋₁₀ cycloalkyl, hydroxylamino, mercapto-amino, alkylamino, cycloalkylamino, alkenylamino, cycloalkenylamino, alkynylamino, arylamino, arylalkylamino, hydroxyalkylamino, mercaptoalkylamino, heterocyclic amino,

hydrazino, alkylhydrazino, phenylhydrazino, sulfonyl, sulfinyl and sulfonamido; or R₆ together with R₇ and the carbon atoms in positions 6 and 7 of the pteridine ring forms a homocyclic or heterocyclic radical;

5 and/or a pharmaceutically acceptable addition salt thereof and/or a stereoisomer thereof and/or a mono- or a di-*N*-oxide thereof and/or a solvate and/or a dihydro- or tetrahydropteridine derivative thereof.

12. The method of claim 11, wherein the patient is a human and wherein said effective amount is within a range of 0.01 to 20 mg per day per kg bodyweight of the patient.

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